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Serial No. 10/677,733

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Applicant: Gardner et al.

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Filed: Oct 01, 2003

Group Art Unit: 1656

Docket No. UTSD:1510

Examiner: Nashed, Nashaat T.

Title: NMR Detection of Foreign PAS Domain Ligands

CERTIFICATE OF TRANSMISSION
I hereby certify that this corr is being transmitted by facsimile to the Comm for Patents at 571-273-8300 on January 28, 2007.

Signature _____
Richard Aron Osman

REPLY BRIEF ON APPEAL

The Honorable Board of Appeals and Interferences
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Honorable Board:

The Answer dated Jan 24, 2007 withdraws the Examiner's rejections under 35USC112, second paragraph; hence, the only remaining issue is the propriety of the Examiner's rejection made under 35USC103(a).

I. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIMS 1 & 2 UNDER 35USC103(a).

Fesik (WO97/18471) discloses the use of particular two-dimensional $^{15}N/^{1}H$ NMR correlation spectra to identify ligands of target biomolecules. Fesik teaches nothing about PAS domains.

Edery (US 5,843,683) characterizes four PAS domain containing proteins (AHR, SIM, ARNT and PER) and use co-immunoprecipitation experiments to propose that PAS domains engage in PAS-PAS interactions. Edery proposes and claims assays for molecules that modulate PAS-PAS interactions.

Takahashi (US 6,291,429) describes circadian clock genes from humans and mice, and proposes contemplated uses of CLOCK polypeptides including use "in a screening assay for the identification of drugs or compounds that inhibit the action of CLOCK polypeptide (e.g., DNA binding)." Takahashi, col.9, lines 13-27.

Berkenstam (US 6,436,654) discloses and claims methods for identifying compounds which modulate the function of a functional domain of a variant of human HIF-1.alpha that lacks at least one functional domain thereof.

Our claims are specifically directed to a method of detecting binding of a PAS domain with a foreign core ligand of the PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity. The method specifically requires the steps of: (a) detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand; and (b) comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain.

As explained in our Specification some members of the PAS family are known to contain small molecule cofactors within their cores, and these cofactors are reportedly required for proper folding and functioning of the PAS domain within the context of the holo-protein. Specification, p.1, line 22 - p.2, line 1. However, for most PAS domains there is no evidence for such a cofactor. In fact, structurally characterized PAS domains without bound cofactors (Amezcua et al., 2002; Erbel et al., 2003; Morais Cabral et al., 1998) show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site. Specification, p.2, lines 2-5. Since the prior work provided no evidence of cofactors for most PAS domains, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have suspected that such PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding; in fact, the art (*supra*) teaches squarely

away from such use.

Though the cited art does not support a prima facie case for obviousness, for good measure we have of record affirmative evidence documenting the fact that one skilled in the art would have considered the claimed invention nonobvious at the time it was made (attached expert Declaration).

The Answer's repeated proclamations that one skilled in the art would have known that the cited art PAS domains "must" contain ligand binding cavities (Answer p.6, lines 16-17; p.7, lines 10-12) are boldly unsubstantiated and contrary to the uncontroverted evidence of record. The Answer's primers on protein folding (Answer p.6, lines 11-16) and NMR (Answer, p.6, line 24- p.7, line 8) confuse a folded protein's hydrophobic core with the recited ligand cavity, and do not evidence a competent analysis of the claimed subject matter and cited art.

Appellants respectfully request reversal of the pending Final Action by the Board of Appeals.

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

Richard Aron Osman, J.D., Ph.D., Reg. No.36,627
Tel (949) 218-1757; Fax (949) 218-1767